APPENDIX 1

IZZO et al.

Importance of Systolic Blood Pressure in Older Americans

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Clinical Advisory Statement

Importance of Systolic Blood Pressure in Older Americans

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This clinical advisory statement from the Coordinating Committee of the National High Blood Pressure Education Program is intended to advance and clarify the recommendations of the Sixth Report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC VI, 1997).[1] The advisory addresses several interrelated issues about blood pressure (BP) that affect people approaching the later decades of life. On the basis of the wealth of currently available evidence, the committee now recommends a major paradigm shift in urging that systolic BP become the major criterion for diagnosis, staging, and therapeutic management of hypertension, particularly in middle-aged and older Americans.

Several lines of strong evidence support the initiative to emphasize systolic BP. Pathophysiologically, there are strong associations among aging, increased stiffness of large arteries, increased systolic BP, increased pulse pressure, and the prevalence of cardiac and vascular disease. Epidemiologically, isolated systolic hypertension is the most common form of hypertension and is present in approximately two thirds of hypertensive individuals >60 years of age. Diagnostically, classification and staging of hypertension are more precise when systolic rather than diastolic BP is used as the principal criterion. Risk stratification for major complications of hypertension (stroke, myocardial infarction, heart failure, and kidney failure) is actually confounded by the use of diastolic BP; in older people with systolic hypertension, diastolic BP is inversely related to cardiovascular risk. Clinical benefits of treatment of isolated systolic hypertension include reductions in stroke, myocardial infarction, heart failure, kidney failure, and overall cardiovascular disease morbidity and mortality.

Currently, only 1 in 4 Americans with hypertension falls below JNC VI–recommended values of 140/90 mm Hg in uncomplicated hypertension or 130/85 mm Hg in individuals with kidney disease or diabetes. Hypertension control rates are poorest in older people, primarily as a result of inadequate systolic BP control. The Coordinating Committee believes that achievement of optimal cardiovascular health in the United States requires a new nationwide initiative to improve our current low rates of systolic BP control. In addition to the recognition of the preeminent role of systolic BP in the management of hypertension, the strategic value of risk stratification and the clinical benefit of vigorous BP management at all ages are reemphasized. The use of age-adjusted BP targets is discouraged.

Current Perspectives in BP Control and Cardiovascular Risk Management

Of the 50 million Americans with hypertension in the United States, only about half are currently treated with antihypertensive drugs and only about a quarter have BP values below the targets of 140 systolic and 90 mm Hg diastolic.[2] Achievement of BP goals is even poorer in older Americans. In hypertensives >70 years of age, 25% of African Americans and 18% of white Americans have achieved the BP goals recommended by JNC VI.[3] These data reveal that clinicians may be willing to treat hypertension but still do not achieve desired goals. Systolic BP is almost always less well controlled than diastolic BP, even in clinical trials, in which aggressive management is required. In the Multiple Risk Factor Intervention Trial (MRFIT) and the Hypertension Optimal Treatment (HOT) trial, diastolic control rates exceeded 90%, whereas systolic control rates were less than 60%.[4,5]

As the US population ages, the burden of uncontrolled systolic hypertension will take an increasing toll on the health and well-being of our society and will contribute to unnecessarily high healthcare costs. Inadequate reduction of systolic BP and dismal systolic BP control rates are causally related to a variety of adverse outcomes. For example, systolic hypertension is the most prevalent risk factor in heart failure,[6] and clinical trials have demonstrated unequivocally that control of systolic hypertension prevents the development of heart failure.[7] Other major cardiovascular disease end points such as stroke and kidney failure also track closely with systolic BP, and in kidney disease, it is clear that lower pressures are associated with better outcomes.[8] Systolic hypertension interacts with other major risk factors such as hypercholesterolemia and diabetes, which also increase in prevalence with age, to amplify the age-related risk of cardiovascular events.[9]

All high-risk populations benefit markedly from vigorous BP control.[10] The importance of vigorous BP control in diabetics is the subject of a companion Clinical Advisory Statement.[11] In all high-risk groups, the number needed to treat to demonstrate benefit (which is reflective of the absolute benefit of treatment) is substantially lower than that in lower-risk groups. In addition to better BP control, aggres-

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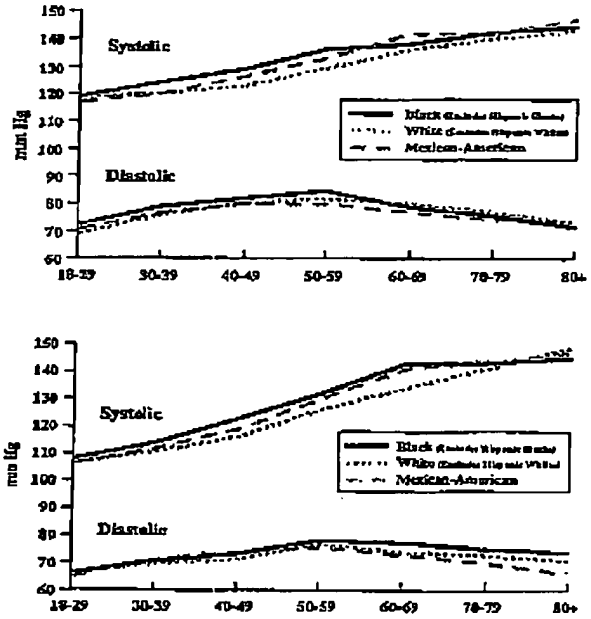

Figure 1. Systolic and diastolic BP by age and race or ethnicity for men and women >18 years of age in US population. Data from NHANES III, 1991 to 1993.[2]

sive management of other common risk factors such as hypercholesterolemia and glucose intolerance are required to achieve optimal cardiovascular benefit at any age.

Age and Pathogenesis of Systolic Hypertension

Systolic BP increases steadily with age in industrialized Western societies, whereas diastolic BP increases until about age 55 years and then declines[2] (Figure 1). Pulse pressure (systolic-diastolic BP difference) therefore widens with age.[12,13] Age-related changes in BP are manifestations of a generalized process of increasing arterial stiffness (or decreasing compliance) that results from the progressive replacement of elastin by collagen in the walls of large arteries.[14] This process of diffuse arteriosclerosis leads to dilatation and lengthening of the aorta and its immediate branches through fibrosis and hypertrophy of the arterial muscularis. Arteriosclerosis inevitably accompanies aging in Western societies, but its development is clearly accelerated by the presence of hypertension and the age at which it is expressed varies with the degree of BP elevation.

Arteriosclerosis can be differentiated pathophysiologically from atherosclerosis, which is primarily related to the effects of abnormal cholesterol oxidation and deposition in the inner layers of large arteries. Atherosclerosis begins as endothelial dysfunction and macrophage uptake of oxidized lipids into the vessel walls and is accelerated by the coexistence of hypertension. It evolves into a patchy, chronic inflammatory process that includes varying degrees of complexity and rupture of cholesterol-laden plaques and eventually, local vascular occlusion or distal embolization.[15]

Because of their close relation to arteriosclerosis, both systolic BP and pulse pressure are reliable markers of age-related vascular target organ damage. Pulse pressure, although slightly more robust than systolic BP as a risk indicator, is considerably less straightforward to use clinically than systolic BP, and it has not yet been validated as a surrogate end point for morbidity or mortality in a prospective randomized clinical trial. Accordingly, this statement focuses on systolic BP rather than pulse pressure.

Systolic Hypertension: Prevalence, Diagnostic Value, and Risk Stratification

The prevalence of hypertension increases with age, with systolic hypertension becoming far more common than diastolic hypertension. In the National Health and Nutrition Examination Survey (NHANES) study, isolated systolic hypertension (systolic ≥140 with diastolic <90 mm Hg) was present in 65% of all hypertensives >60 years of age, whether male or female.[16] The accuracy of diagnosis and staging of hypertension according to JNC VI guidelines is markedly improved by using systolic rather than diastolic BP. Applying JNC VI definitions of hypertension (stage 1 hypertension: BP ≥140 systolic or ≥90 diastolic, stage 2 hypertension: ≥160 systolic or ≥100 diastolic, stage 3 hypertension: ≥180 systolic or ≥110 mm Hg diastolic) to the Framingham cohort, those with high normal BP or hypertension, who were potential candidates for antihypertensive therapy, were correctly classified by systolic BP alone 91% of the time. In contrast, correct BP classification occurred in only 22% of these individuals when diastolic BP was used alone.[17]

Systolic BP and pulse pressure are closely related independent cardiovascular disease risk factors[13,18] that yield similar diagnostic and prognostic information. It has been known since the early reports from Kannel and colleagues[19] at the Framingham Heart Study that systolic BP is more robust than diastolic BP as a cardiovascular disease risk factor, a phenomenon recently emphasized by Dustan.[20] More recent data from Framingham clearly reinforce the prognostic significance of elevated systolic BP and wide pulse pressure as independent risk factors.[13] In

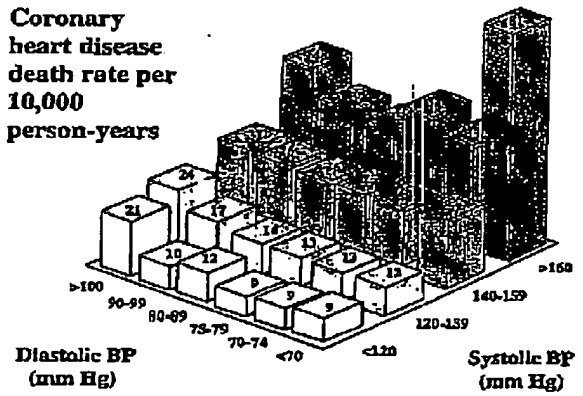

Figure 2. Relation of systolic and diastolic BP to death from coronary heart disease in MRFIT. Data compiled from >316 000 male screenees followed for 12 years. Adapted from Neaton et al.[4]

Major Trials in Isolated Systolic Hypertension

	n	Age	Entry BP	Relative Risk Reduction, %			
				Stroke	CAD	CHF	All CVD
SHEP	4736	≥60	171/77	−33	−27	−55	−32
Syst-EUR	4695	≥60	174/86	−42	−26	−29	−31

SHEP indicates Systolic Hypertension in the Elderly Program[22]; Syst-EUR, European Trial in Systolic Hypertension[7]; CAD, coronary artery disease; CHF, congestive heart failure; and CVD, cardiovascular disease.

people >60 years of age, when systolic BP is >120 mm Hg, diastolic BP is inversely related to cardiovascular disease risk.[13] Thus, an individual whose BP is 160/70 is at greater risk than an individual whose BP is 160/100 mm Hg.

The preeminent value of systolic BP in risk prediction is even more convincingly demonstrated in 12-year data from >316 000 men screened for MRFIT.[4] As demonstrated in this large cohort (Figure 2), coronary heart disease death rates were almost linearly related to systolic BP at all levels of blood pressure. In MRFIT, increased cardiovascular disease risk in those with systolic BP <140 mm Hg was found only when diastolic BP exceeded 100 mm Hg.[4] With respect to the risk of kidney failure, the MRFIT database revealed that although both systolic and diastolic BP were important, systolic BP was the more precise risk indicator.[21]

Clinical Trial Benefits of Systolic BP Control

Compelling data from 2 large clinical trials directly demonstrate the benefits of treating isolated systolic hypertension (Table). The SHEP (Systolic Hypertension in the Elderly Program) study,[22] a placebo-controlled, double-blind, randomized trial, investigated the value of thiazide diuretic–based treatment in 4736 individuals >60 years of age with isolated systolic hypertension (initial BP values ≥160 mm Hg systolic and <90 mm Hg diastolic). After 5 years of therapy, active treatment with diuretic, with or without β-blockers, reduced average systolic BP values ≈14 mm Hg more than placebo, with an overall systolic BP reduction from 171 to 142 mm Hg. Compared with placebo, those randomized to diuretic treatment had marked reductions in the rates of myocardial infarction (−27%), heart failure (−55%), and stroke (−37%) as well as exhibiting trends toward improvement in depression and dementia scores. A large randomized European trial of isolated systolic hypertension (Syst-EUR) used dihydropyridine calcium antagonist–based therapy and found reductions in systolic BP and cardiovascular outcomes similar to those in SHEP.[23]

Optimal Control Strategies: BP Targets and Drug Effects

Epidemiological data demonstrate that cardiovascular disease morbidity and mortality is roughly proportional to systolic BP across a very wide range of BP values. Thus, from the perspective of early treatment and disease prevention, the systolic BP target of 140 mm Hg that has been established from observational data remains fully justifiable. From the perspective of treatment of those with established hypertension, however, the question of how low to go remains open. If therapeutic benefit in systolic hypertension follows the observational data, the greater the decrease in BP, the less the risk. SHEP and Syst-EUR demonstrated that lowering systolic BP to <160 mm Hg is markedly beneficial,[7,22] but no trial has directly measured the degree of additional benefit that would occur at a systolic BP target <140 mm Hg.

Also currently unanswered is the question of whether all antihypertensive drug classes confer equal benefit or whether some agents offer therapeutic benefits beyond BP control. In isolated systolic hypertension, JNC VI recommended diuretics and calcium antagonists for isolated systolic hypertension, with diuretics preferred because of the convincing clinical trial data indicating protection against myocardial infarction, heart failure, and stroke. A recent study, the second Swedish Trial in Old People with Hypertension (STOP Hypertension-2), was conducted in individuals with stage 3 hypertension whose pretreatment and posttreatment BP values were ≈190/100 and 160/80 mm Hg, respectively.[24] No additional benefits were claimed for "newer" drugs (low-dose angiotensin-converting enzyme [ACE] inhibitors or calcium antagonists) compared with a standard diuretic–β-blocker regimen, but the data showed ACE inhibitors to be superior to calcium antagonists (23% better against myocardial infarction and 22% better against heart failure). The Heart Outcomes Prevention Evaluation (HOPE) trial, carried out over a period of 4 years in >9000 high-risk individuals >60 years of age, reported that ACE inhibition reduced the combined incidence of myocardial infarction, stroke, and death by ≈22%.[25] The authors found that ACE inhibition conferred equal benefit in both hypertensive and normotensive individuals when compared with placebo and suggested that the small BP decreases that were observed (≈3/2 mm Hg) could not fully account for the cardiovascular benefits of ACE inhibition. In HOPE, however, BP measurements were sporadic and unstandardized. The attractive possibility of enhanced benefits with certain antihypertensive drug classes therefore remains open.

Recommendations

In any form of hypertension, the primary goal is to lower BP by using any approved antihypertensive agent that is effective, well tolerated, and appropriate for the spectrum of clinical conditions present in the individual under treatment. JNC VI clearly stated that individualized therapeutic strategies were most desirable and that the skill and judgment of individual clinicians were essential in achieving optimal outcomes. JNC VI was predicated on the idea of integrated management based on risk stratification. It highlighted the roles of comorbidities in the decision-making process and identified high-risk conditions in which clinical trial evidence has provided "compelling indications" for the use of certain drug

classes. In isolated systolic hypertension, thiazide diuretics (with or without β-blockers) and long-acting calcium antagonists are recommended on the basis of the results of SHEP and Syst-EUR. Lifestyle changes remain useful adjuncts in helping older patients achieve BP goals.

On the basis of the foregoing arguments, the Committee has specifically recommended: (1) Systolic BP should become the principal clinical end point for the detection, evaluation, and treatment of hypertension, especially in middle-aged and older Americans. (2) The importance of lifelong maintenance of BP <140/90 mm Hg is reaffirmed on the basis of the known favorable risk-benefit balance at this level. Foremost in this assertion is the need for early therapy as primary protection against target organ damage. It should also be recognized that BP control (especially systolic) remains valuable at any age, initial BP level, or duration of hypertension. (3) More stringent BP control is necessary to achieve optimal benefit in high-risk conditions. In hypertensives with diabetes, BP should be maintained <130/85 mm Hg and in hypertensives with kidney failure or heart failure, BP should be reduced to the lowest levels possible. (4) Age-adjusted BP targets are inappropriate, including the unsubstantiated but persistent clinical folklore that it is acceptable for systolic BP to be "100+your age." (5) ACE inhibitors are recommended as agents that lower morbidity and mortality rates in older people, in whom systolic hypertension is most prevalent.

The vast majority of hypertensive individuals can achieve recommended BP targets without significant difficulty. It is acknowledged, however, that clinicians should proceed with caution in treating certain elderly individuals with long-standing severe systolic hypertension, in whom rapid lowering of BP may be difficult or possibly harmful. In brittle or truly resistant patients, it may be wise to allow longer periods of time to reach goal BP. Although it is reasonable to assume that partial BP control is preferable to none at all, it is also clear that "lower is better" in the vast majority of patients.

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